

# The role of hyperbaric oxygen therapy in inflammatory bowel disease: a narrative review

Xin Wu<sup>‡</sup>, Tian-Yu Liang<sup>‡</sup>, Zhong Wang<sup>\*</sup>, Gang Chen

Department of Neurosurgery & Brain and Nerve Research Laboratory, the First Affiliated Hospital of Soochow University, Suzhou, Jiangsu Province, China

\*Correspondence to: Zhong Wang, MD, wangzhong761@163.com.

<sup>‡</sup>These authors contributed equally to this work.

orcid: 0000-0002-7342-0845 (Zhong Wang)

## Abstract

Inflammatory bowel disease is a group of chronic recurrent diseases in the digestive tract, including ulcerative colitis and Crohn's disease. Over the past few decades, the treatment of IBD has made great progress but there is still a lot of room for improvement. Hyperbaric oxygen therapy (HBOT) was defined as the therapeutic effect of inhaling 100% oxygen higher than one atmosphere and reported to be used in stroke, decompression sickness and wound healing. Since several authors reported the role of HBOT as an adjunct to conventional medical treatment in patients with refractory IBD, the relevant research has shown an increasing trend in recent years. Clinical and experimental studies have revealed that HBOT may exert its therapeutic effect by inhibiting inflammation and strengthening the antioxidant system, promoting the differentiation of colonic stem cells and recruiting cells involved in repair. The purpose of this review is to summarize the past clinical and experimental studies and to understand the impact of HBOT in the treatment of IBD more deeply. In addition, we also hope to provide some ideas for future clinical and research work.

**Key words:** anti-inflammatory; anti-oxidation; clinical and experimental studies; Crohn's disease; hyperbaric oxygen therapy; inflammatory bowel disease; oxygen; therapeutic implications; ulcerative colitis

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## INTRODUCTION

Inflammatory bowel disease (IBD) is an intestinal inflammatory disease that invades the ileum, rectum, and colon and includes ulcerative colitis (UC) and Crohn's disease (CD). It is a chronic recurrent disease with clinical manifestations of diarrhea, abdominal pain, bloody stools and inflammation involving the digestive tract. Over the past few decades, the treatment of IBD has made great progress from the conventional clinical treatments including aminosalicylates, oral immunomodulators, and corticosteroids, to the use of tumor necrosis factor (TNF) inhibitors such as infliximab, adalimumab, and golimumab in recent years.<sup>1-3</sup> However, the damage of immunomodulators to immune function and the adverse events of long-term use of corticosteroids, coupled with the fact that more than 40% of patients are irresponsive to TNF inhibitors or develop late drug resistance,<sup>4,5</sup> there is still a lot of room for improvement in the prevention and treatment of IBD, especially its complications.

Hyperbaric oxygen therapy (HBOT), defined as the therapeutic effect of inhaling 100% oxygen higher than one atmosphere which can increase the content of oxygen dissolved into the plasma and tissue. HBOT can rapidly increase the concentration of oxygen in the blood reaching hypoxia tissue to release oxygen and treat many ischemic and hypoxic diseases such as gas poisoning, brain hypoxia, decompression sickness and so on. In recent years, HBOT has also revealed its role in wound healing, anti-infections and promoting brain injury through the anti-oxidative effect and the capability to promote neovascularization.<sup>6-8</sup> At the same time, HBOT can

also down-regulate the production of pro-inflammatory factors and chemokines, which play a vital role in the intestinal microenvironment of IBD, in the process of inflammatory activation.<sup>9-11</sup>

Thirty years ago, Brady et al.<sup>12</sup> reported a case in which HBOT was used as an auxiliary means to carry out standard treatment for CD patients and achieved good therapeutic effect. Therefore, increasing clinicians and researchers pay attention to the role of HBOT in IBD. We have searched "hyperbaric oxygen therapy" and "inflammatory bowel disease" or "Crohn's disease" or "ulcerative colitis" in all fields on PubMed with no time limitations. The purpose of this review is to summarize the past clinical and experimental studies, to better understand the impact of HBOT in the treatment of IBD, and hope to provide some ideas for future clinical or research work.

## CLINICAL STUDY ON THE ROLE OF HYPERBARIC OXYGEN THERAPY IN CROHN'S DISEASE

CD is a subtype of IBD, which is a transmural inflammatory disorder that often occurs at the end of the ileum. The etiology of this disease has not been determined, and some studies have pointed out that the disease is caused by the imbalance between pro-inflammatory factors and anti-inflammatory factors resulting from the interaction among heredity, immunity and environment.<sup>13,14</sup> Patients with CD often perform heterogeneous clinical manifestations vary from abdominal pain, diarrhea, intestinal obstruction to other parenteral manifestations like fever, nutritional disorders. Since there is no



fundamental cure for the disease at present, most treatments aim to induce and maintain the disease in chronic remission by controlling inflammation.

The role of hypoxia as a pathogenic factor has been assumed in the occurrence and maintenance of inflammation. Study has shown that hypoxia is an important trigger for inflammation.<sup>15</sup> HBOT as an option that can increase blood oxygen concentration and correct tissue hypoxia rapidly was first used as an adjuvant therapy in the treatment of CD in 1989.<sup>12</sup> A 48-year-old woman who suffered from CD was responded to hyperbaric oxygen dramatically. She received a total of 67 hyperbaric oxygen treatments in more than 2.5 months and her lesions completely healed after the last treatment. Another case report about 1 year later also reported a 49-year-old male patient with CD who successfully integrated HBOT into her treatment regimen and achieved a complete and sustained healing.<sup>16</sup> Since then more attention has been paid on the role of HBOT in CD, especially in the treatment of its complications.

Perianal CD, as a frequent and troublesome complication of CD, can seriously increase patients' suffering and is associated with a huge psychological, economic and social burden.<sup>17</sup> Penner and Crohn<sup>18</sup> first described the disease in 1938, in author's explanation, the disease can present as the progressive lesions such as painless anal fissures, multiple anal fistula, abscesses and ulcer that cannot completely healing by medical and surgical interventions. More than 43% of patients with CD eventually develop perianal disease, and proximately 5% of the patients even have perianal lesions as their only clinical manifestation.<sup>19</sup> The best outcome of treatment is complete closure with no infection, abscess, or recurrence, but unfortunately, the success rate of traditional medicine and surgical treatment is range from 30% to 80% as reported.<sup>20</sup> Then a clinical trial included 10 patients with CD who had perianal invasion and did not respond to conventional treatment was undertook to evaluate the efficacy of HBOT.<sup>21</sup> Patients received a maximum of three courses HBOT treatment and each course consisted of 20 daily sessions (hyperbaric oxygen for 90 minutes at a pressure of 253 kPa). The results showed that perianal lesions of eight patients completely healed (three of them healed within only one single course), and only two patients did not respond to the therapy. Another clinical trial involving seven patients yielded similar results (five of them were completely cured).<sup>22</sup> Moreover, the authors also collected the blood samples from these patients in five different time points (before/after the first course of treatment, before/after the second course of treatment and after the last course of treatment) to detect the level of pro-inflammatory factors interleukin (IL)-1, IL-6 and TNF- $\alpha$ . The results showed that HBOT could significantly reduce the secretion of these three pro-inflammatory factors, which may provide evidence for the treatment of inflammatory diseases with HBOT. More interestingly, a clinical study by Fraser and Niv<sup>23</sup> revealed that this therapeutic effect of HBOT may not require a dedicated hyperbaric oxygen chamber, but also can be achieved in an environment with elevated oxygen pressure. They sent six patients with perianal CD who were resistant to the conventional treatment to the Dead Sea environment (the lowest point on the earth, 402 m below sea level, so the partial pressure of oxygen is the highest) for 3 weeks followed what

the patients obtained improvement in their disease and even one of them got completely healing. To sum up, although could not achieve a complete healing for every patient, there is no doubt about the role of HBOT in the treatment of perianal CD.

HBOT is also effective for other complications of CD except for perianal wound. A clinical trial included fourteen patients with enterocutaneous fistulas, perineal CD or pyoderma gangrenosum who considered refractory to pharmacological therapy treated with HBOT.<sup>24</sup> Eleven of all the patients in this clinical trial had satisfactory results, which included five patients with enterocutaneous fistulas and two patients with pyoderma gangrenosum. Five years later, another similar clinical trial recruited 29 patients with refractory CD who were submitted to daily sessions of HBOT.<sup>25</sup> Results showed that 22 of all the patients had satisfactory improvements and the successful healing rates of pyoderma gangrenosum, enterocutaneous fistulas and perineal CD were respectively 100%, 91% and 65%, revealing that HBOT is more effective for the former two diseases. HBOT not only has an effect on the extraintestinal complications of CD, but may also have an effect on intestinal lesions. Takeshima et al.<sup>26</sup> reported a 16-year-old girl diagnosed with CD and found a deep longitudinal ulcer in the rectum under colonoscopy. They developed a combination therapy that included hyperbaric oxygen, steroids and sulfasalazine. After 20 sessions of hyperbaric oxygen, the ulcer healed to scar tissue successfully under colonoscopy. The efficacy of HBOT in the treatment of intestinal lesions is significant, but more clinical and laboratory studies are still needed.

Studies in recent years have shown that the use of multiple combination therapy contained HBOT may have gratifying therapeutic effects. Ten patients with severe perineal CD were treated with HBOT in a clinical trial by Colombel et al.<sup>27</sup> With the exception of 2 patients who dropped out for other reasons at first, the other 8 received a total of 40 sessions HBOT for 4 weeks and 6 of them got improvement with their lesions. The authors also found that combine HBOT with local surgical procedures might be an attractive way to treat such disease due to its perfect healing rate. Agrawal et al.<sup>28</sup> used a novel combination therapy included infliximab, anti-MAP and HBOT to treat nine patients who failed to heal perianal fistulae on conventional treatment including anti-TNF and, impressively, 100% of the patients achieved a complete response. A clinical trial focused on persistent perineal sinus, a common complication following proctectomy for IBD also found the advantages of HBOT. Four patients with extreme persistent perineal sinus received HBOT before or after abdominoperineal persistent perineal sinus excision combine with perineal reconstruction with vertical or transverse rectus abdominis myocutaneous flap repair surgery, then complete healing occurred in all patients within 3 months.<sup>29</sup> Therefore, it is still necessary to conduct further research on the treatment methods of CD combined with HBOT and other treatments.

## CLINICAL STUDY ON THE ROLE OF HYPERBARIC OXYGEN THERAPY IN ULCERATIVE COLITIS

UC is a chronic disease characterized by intermittent recurrence and remission, which often leads to colonic and rectal ulcers. The cause is still controversial, and current studies tend



to be the incorrect immune responses to their own intestinal microenvironment of individuals with genetic susceptibility.<sup>30</sup> Although most patients with UC are in the mild to moderate stage, about one-fifth of them will be hospitalized after a severe acute exacerbation at least once in their lifetime.<sup>31</sup> Treatments vary for different stages of UC, ranging from 5-aminosalicylic preparations for mild to moderate patients to steroids for severe acute episodes patients, and to the patients who are not sensitive to steroids need to be treated with cyclosporine, methotrexate. Despite such drug interventions, for acute severe UC, a mode of presentation about 10% of the patients, the failure rate can reach 40–50% within 3 months of hospitalization and rise to 70% within 3 years.<sup>32</sup> Moreover, a 27% of postoperative complications rate including physical and psychological complications after colectomy coupled with a 5.3% postoperative mortality rate within 90 days under emergency status, make the surgical treatment of UC unsatisfactory.<sup>33,34</sup> Therefore, the discovery of a new treatment method that is effective for the patients with severe UC and has little side effects is the desire of many clinicians.

As mentioned above, the application of HBOT in CD was as early as 1989, while the application in UC was later mentioned in two case reports at the beginning of the 21<sup>st</sup> century. A 24-year-old male patient with pan-colonic UC had a history of two previous hospitalizations for exacerbations, and the third exacerbation had lasted for 22 months and was resistant to conventional therapies. After 30 sessions of HBOT on a five times per week basis, the patient got improvements both of clinical symptoms and quality of life indicated by the Truelove-Witts score and the IBD questionnaire score, and follow-up after discharge showed that his clinical remission lasted for 2 months.<sup>35</sup> Another case reported 2 years later, a 52-year-old female patient with relapsing UC who failed to the treatment of 5-amino salicylic acid, methylprednisolone, and azathioprine. With the use of HBOT for 35 days, the patient was asymptomatic and her clinical remission lasted up to 6 months.<sup>36</sup> Although the authors of these two case reports both have found that HBOT has little effect on the severity of intestinal lesions observed under colonoscopy, it is undeniable that it plays a role in inducing clinical remission in patients with severe UC. For those patients in clinical remission, HBOT has also been reported to have the ability to treat rare complications of UC such as pyoderma gangrenosum. As a rarely observed complication of UC, the prevalence of pyoderma gangrenosum is only about 2% but is a kind of clinical suffering for patients.<sup>37</sup> A 65-year-old male patient with a 17-year history of UC and is in clinical remission but with a painful skin defect in both shins at the time of hospitalization. After 3 months of medical intervention including HBOT, the ulcer lesions in both pretibial areas have been completely healed.<sup>38</sup> Generally speaking, from the point of view of these case reports, the clinical efficacy of HBOT in patients with UC is worthy of affirmation, and at the same time, it is necessary to conduct large-scale, multi-person clinical trials to make the results more convincing.

Recently, a prospective case series reported the role of HBOT on refractory UC and explored its underlying mechanism. Patients who were no response for 5 weeks of continu-

ous medical therapy were treated with HBOT and the authors collected their clinical and histopathological scores to evaluate the efficacy of the treatment. The results shows that HBOT proved to be effective for bring clinical improvement and reduce disease activity to patients. Moreover, HBOT could promote mucosal healing, and the authors attributed this effect of HBOT to an increase in the number of stem cells in the colonic mucosa observed in the study.<sup>39</sup> It has been reported that HBOT can mobilize vasculogenic stem cell from bone marrow of patients with diabetes and recruit more cells to skin wounds to promote healing.<sup>40</sup> Therefore, in patients with UC, HBOT may also mobilize bone marrow stem cells to differentiate into colonic mucosal cells and recruit more cells to participate in the repair process of mucosal ulcers. On this basis, the results of another multi-center, randomized, double-blind sham-controlled study further confirmed the clinical effect of HBOT. Ten patients in the controlled group were given steroids + HBOT therapy, while eight patients in the sham group were given steroids + sham hyperbaric air therapy. The results showed that patients in the HBOT-treated group achieved faster clinical remission, and the proportion of patients who developed to require second-line treatment and colectomy was much lower than that in the sham group.<sup>41</sup> But on the contrary, a prospective study conducted by Pagoldh et al.<sup>42</sup> on patients with severe UC found no statistically significant differences between HBOT plus conventional therapy group and conventional therapy alone group. The authors gave standard intensive glucocorticosteroid treatment and glucocorticosteroid + HBOT treatment to the control group and the intervention group respectively, and took clinical outcome, the laboratory results and fecal weight as short-term indicators, and took health related quality of life, colectomy rate and evaluation of HBOT safety as long-term indicators. The results revealed that HBOT intervention did not show a positive effect on these indicators and the lack of positive results may be related to the small number of samples in the study.<sup>42</sup> In short, despite some controversial results, HBOT is undoubtedly a good supplement to conventional therapy for patients with UC, not only its ability to increase the oxygen supply to the ischemic digestive tract, but also its ability to promote the migration of stem cells and other cells, indicating that it has great therapeutic potential and research value.

## EXPERIMENTAL STUDY ON THE ROLE OF HYPERBARIC OXYGEN THERAPY IN INFLAMMATORY BOWEL DISEASE

All the clinical studies of HBOT in IBD involved in this paper are summarized in **Table 1**. Compared with clinical studies, the experimental studies of HBOT in IBD are much less. Oxidative stress is a sign of cell death and increasing evidence have shown that the increase or untimely clearance of oxidative stress products will lead to tissue damage. At the same time, HBOT has been revealed to down-regulate oxidative stress levels in the treatment of other diseases.<sup>43</sup> Superoxide dismutase and glutathione peroxidase are two enzymes that control cellular defense mechanisms and can regulate the level of intermediate reduction products of oxygen metabolism.<sup>44,45</sup> Gulec et al.<sup>46</sup> used an acetic acid-induced colitis model on rats

**Table 1: A summary of HBOT in IBD**

Author	Study design	Indication	HBOT parameters			Number of patients improved/involved	Side effects
			ATM	Treatment time (min)	Total number of sessions		
Brady et al. <sup>12</sup>	Case report	CD	2.4	120	67	1/1	Blurred vision
Nelson et al. <sup>16</sup>	Case report	CD	2	120	44	1/1	Not reported
			2.8	90	30		
Lavy et al. <sup>21</sup>	Clinical trial	CD	2.5	90	60	8/10	None
Weisz et al. <sup>22</sup>	Clinical trial	CD	2.5	90	40	7/7	None
Iezzi et al. <sup>24</sup>	Clinical trial	CD	2.4	120	10–50	11/14	None
Feitosa et al. <sup>25</sup>	Clinical trial	CD	2.4	120	10–86	22/29	None
Takeshima et al. <sup>26</sup>	Case report	CD	2.8	120	20	1/1	Not reported
Colombel et al. <sup>27</sup>	Clinical trial	CD	2.5	120	40	6/8	Bilateral eardrum perforation
Agrawal et al. <sup>28</sup>	Clinical trial	CD	2.0–2.4	90	18–30	9/9	None
Chan et al. <sup>29</sup>	Clinical trial	CD	2.2–2.4	90	30	4/4	None
Buchman et al. <sup>35</sup>	Case report	UC	2	120	30	1/1	Not reported
Gürbüz et al. <sup>36</sup>	Case report	UC	2	120	35	1/1	Not reported
Seo et al. <sup>38</sup>	Case report	UC	2.4	120	30	1/1	Pain in the left ear
Bekheit et al. <sup>39</sup>	Prospective case series	UC	2.8	60	40	32/32	None
Dulai et al. <sup>41</sup>	Clinical trial	UC	2.4	90	10	8/10	None
Pagoldh et al. <sup>42</sup>	Prospective randomized study	UC	2.4	90	30	4/10	Abnormal middle ear pressure

Note: ATM: Atmosphere; CD: Crohn's disease; HBOT: hyperbaric oxygen therapy; IBD: inflammatory bowel disease; UC: ulcerative colitis.

to evaluate the effect of HBOT on anti-oxidation system products included superoxide dismutase, glutathione peroxidase and malondialdehyde, one of the reduction products of oxygen metabolism. The authors found that compared with the colitis group, the level of glutathione peroxidase in the hyperbaric oxygen-treated group were significantly increased in colonic tissue, plasma and erythrocytes, while the level of malondialdehyde was significantly decreased contrarily. Meanwhile, the level of superoxide dismutase in colonic tissue in hyperbaric oxygen-treated group was significantly higher than that in colitis group. This suggests that HBOT does play a beneficial role in enhancing the antioxidant system in experimental colitis, especially in the colonic tissue. Tissue myeloperoxidase levels are often used to detect neutrophil aggregation in inflammatory tissues and have previously been shown to be positively correlated with the number of neutrophils in colonic tissue measured by histochemical methods.<sup>47</sup> Some studies in the model of experimental colitis have compared the anti-inflammatory effects of HBOT with 5-aminosalicylic acid and dexamethasone, two commonly used drugs for the treatment of IBD by detecting the levels of myeloperoxidase.<sup>48,49</sup> Interestingly, on the one hand, although the effect of HBOT on reducing the activity of myeloperoxidase is lower than 5-aminosalicylic acid, HBOT can greatly enhance such effect of 5-aminosalicylic acid; on the other hand, although the effect of reducing myeloperoxidase activity of HBOT is higher than dexamethasone, there is no significant statistical difference between the combination of the two treatments and the use of single therapy. Therefore, more experimental and even clinical studies are needed to determine which treatment

is the most effective and beneficial for the patients.

## MECHANISMS UNDERLYING THE THERAPEUTIC EFFECT OF HYPERBARIC OXYGEN THERAPY

As described above in this article, the mechanisms underlying the therapeutic effect of HBOT in the treatment of IBD are summarized as follow: (1) HBOT can increase colonic tissue oxygen levels and the blood oxygen concentration of supplementary vessels; (2) HBOT can inhibit inflammatory response by inhibiting the release of pro-inflammatory cytokines such as IL-1, IL-6 and TNF- $\alpha$ ; (3) HBOT can promote the differentiation of colonic stem cells and recruit cells involved in repair process; (4) HBOT can enhance the anti-oxidant system and reduce the neutrophil aggregation in the colonic tissue.

## LIMITATIONS

Certainly, there are some limitations to the existing studies and reports summarized in this paper. Firstly, the number of patients included in most clinical trials is insufficient. As shown in **Table 1**, only 3 clinical trials enrolled more than 10 patients, which make the final conclusion lack of universality and persuasion to some extent. Secondly, due to the different parameters of different hyperbaric oxygen chambers, the existing HBOT treatment protocols do not have a unified standard. At the same time, there is also a lack of research on the most appropriate pressure, duration and total session numbers of HBOT. Thirdly, most patients are followed up only for a short period of time during or after treatment. Therefore, the long-term safety and impact of HBOT on disease severity are still unclear.





## CONCLUSION AND FUTURE PROSPECTS

As a chronic disease with no radical cure, long course of IBD is accompanied by increased patient suffering. So it is particularly important to find a safer and more effective treatment. As literature suggested, HBOT is a relatively safe and potentially effective treatment, at the same time, it is also a good supplement to the conventional treatment.<sup>50</sup> This article also confirms this concept through the summary of past clinical and experimental studies. However, there are still many aspects worthy of further study. For one thing, although have enough case reports, more randomized, blinded, controlled clinical trials are needed to confirm the true benefit of HBOT. For another thing, to develop a standardized treatment plan for HBOT with the best outcome is needed as soon as possible. Last but not least, for the patients with IBD, the specific mechanisms underlying the therapeutic effect of HBOT are still unclear due to the lack of experimental studies.

### Author contributions

Writing the manuscript: XW; revision: XW, TYL; drafting: ZW and GC. All the authors read and approved the final version of the manuscript for publication.

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